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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,762	09/05/2003	Charles R. Cantor	701586-053023	6905
50607	7590	11/21/2007		
RONALD I. EISENSTEIN 100 SUMMER STREET NIXON PEABODY LLP BOSTON, MA 02110			EXAMINER KIM, YOUNG J	
			ART UNIT 1637	PAPER NUMBER
			MAIL DATE 11/21/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/655,762

Applicant(s)

CANTOR ET AL.

Examiner

Young J. Kim

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 September 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 10-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 10-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application.
- ☐ Other: _____

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DETAILED ACTION

The present Office Action is responsive to the Amendment received on September 10, 2007.

Preliminary Remark

Claims 4-9 and 14 are canceled.

Claims 1-3 and 10-13 are pending and are under prosecution herein.

Claim Rejections - 35 USC § 103

The rejection of claims 5-8 and 14 under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102), made in the Office Action mailed on March 8, 2007 is withdrawn in view of the Amendment received on September 10, 2007, canceling the rejected claims.

Rejection, Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 1-3 and 10-13 under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102), made in the Office Action mailed on March 8, 2007 is maintained for the reasons already of record.

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Applicants' arguments presented in said Amendment received on September 10, 2007 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments," section.

The Rejection:

Becker et al. disclose a method of measuring the amount of target nucleic acid sequence in a biological sample, comprising the steps:

a) preparing a sample by adding known amount of a standard nucleic acid, wherein said standard nucleic acid has a single nucleotide sequence difference from the target nucleic acid (page 9437, bottom paragraph, in the phrase, "mutated cDNA serves as internal standard"; and page 9438, 2nd paragraph; Figure 1);

b) amplifying the sample of step (a) (see Figure 1, via PCR);

c) using a further method to enhance the difference between the standard and the target nucleic acid sequence at the site resulting in enhanced products so that the difference created by the at least one base between the standard and the target nucleic acid can be detected (the digestion step of Figure 1 which enhances the difference between the standard and the target nucleic acid);

d) quantifying the enhanced products of step (c) by measuring the ratio of the amplified target nucleic acid to the amplified standard nucleic acid to measure the amount of target nucleic acid present in the sample (Figure 2; page 9442, bottom paragraph).

The target nucleic acid is mRNA (page 9437, 2nd paragraph).

The enhancement is achieved via an enzyme which specifically cleaves at the site of differentiation (*Eco*RI digestion; page 9442, bottom paragraph).

Becker et al. do not employ mass spectrometry in their quantification method (claims 4 and 8).

Becker et al. do not explicitly disclose a method of performing primer extension at the site of differentiation (claim 5), or allele-specific hybridization at the site of differentiation (claim 7).

Becker et al. do not explicitly disclose that the method measures the amount of at least 5, 10, 25, or 50 target nucleic acid sequences using at least 5, 10, 25, or 50 standard nucleic acids, respectively (claims 10-13).

Amexis et al. disclose a method of quantifying a target nucleic acid in a sample, in particular, RNA virus (thus infectious agent), wherein the method comprises the steps of:

- a) amplification of a target nucleic acid with a pair of primers (Figure 1B; page 12098, 2nd column, 3rd paragraph);
- b) amplifying the amplified product with MassExtend primers which is specific for a point mutation (Figure 1B; page 12098, 2nd column, 3rd paragraph (middle)); and
- c) detecting and quantifying the amplified products (Figure 1B; page 12098, 2nd column, 3rd paragraph (bottom); Abstract; page 12098, 1st column, 3rd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Becker et al. and with the teachings of Amexis et al., thereby arriving at the claimed invention for the following reasons.

The method employed by Becker et al., which is drawn to the amplifying the target nucleic acid and the standard nucleic acid (which contains a single nucleotide mutation) via use of primers which flank the target nucleic acid region, employs more than a decade old technique – that is – restriction digest, electrophoresis, followed by the radiolabeled (³²P) quantitation method.

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a non-radioactive method of accurately quantitating the target nucleic acid, such as MALDI-TOF, thereby arriving at the claimed invention.

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One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings since methods of quantification employing mass spectrometry, such as SNUPE (single nucleotide primer extension), have been well-established. Given the fact that Amexis et al. amplify a known target nucleic acid sequence via use of a flanking primer pairs, followed by the mutation-specific primer extension, one of ordinary skill in the art would have recognized that the amplification products of Becker et al., would have served equally well for the mutation-specific primer extension, which would have been necessary for the subsequent mass spectrometric analysis.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants traverse the rejection.

Applicants state that both Becker and Amexis are looking at a single target in a uniplex reaction (page 5, 7th paragraph, Response), whereas the instant application is drawn to a method which involves at least two target nucleic acid sequences and a known amount of at least two standard nucleic acids.

Preliminarily, at least two target nucleic acid sequences and at least two standard nucleic acids in no way precludes said two target nucleic acid sequences from having the same sequence.

In other words, the methods disclosed by both Becker and Amexis involves more than a single molecule of a target nucleic acid and a single molecule of standard nucleic acid. Hence, the methods disclosed by both Becker and Amexis clearly comprises at least two same target nucleic acids and at least two same standard nucleic acids.

In addition, even if, *arguendo* that the phrase, “at least two target nucleic acid sequences” and the phrase, “at least two standard nucleic acids” were interpreted to mean “different” nucleic acids

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and “different” standard nucleic acids, it is respectfully submitted that such modification would have been obvious to one of ordinary skill in the art at the time the invention was made and said one of ordinary skill in the art would have had a reasonable expectation of success at arriving at the claimed invention.

Applicants’ arguments and Declaration solely rely on their assertion that multiplexing of multiple targets in a single reaction is not taught by Amexis et al. nor Becker et al.

Preliminarily, it is respectfully submitted that variant nucleic acid can, in fact be considered a different target nucleic acid. One form of variant requires comprises a different nucleic acid sequence, and thus can clearly be considered “different” target nucleic acid.

Secondly, though not acquiescing to Applicants’ interpretation of the term, “different target,” even if the term were to be interpreted according to Applicants’ interpretation, it is respectfully submitted that multiplex detection of different target nucleic acids (i.e., different markers) via MALDI-TOF was known prior to Applicants’ filing of the application.

“A main advantage of MALDI-TOF MS-based genotyping is its ability to multiplex many primer extension assays within a single sample. . . Multiplex PCR and primer extension assays were performed for the CP450 polymorphism and a polymorphism in human LDLR region by amplifying homozygote and heterozygote samples. Multiplex PCR products from heterozygous mutant and homozygote samples were combined . . . and the mixture was genotyped. The data show unambiguous detection of the low-abundance alleles for both loci tested. A quantitation study was not performed for the multiplex experiments; however, the data are presented here to provide a basis for future investigation.” (page 625, Ross et al., “Quantitative Approach to Single-Nucleotide Polymorphism Analysis Using MALDI-TOF Mass Spectrometry,” BioTechniques, September 2000, vol. 29, pages 620-629)

Clearly, one of ordinary skill in the art at the time the invention would have been motivated to multiplex different target nucleic acids in a method combined from Becker et al. and Amexis et al., as the desire and knowledge to multiplex in assays involving MALDI-TOF is clearly evidenced by Ross et al.

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“A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under 103.” (from *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007, Supreme Court) at 1397).

As to whether one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings, it is respectfully submitted that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at producing the combination of teachings given the fact that multiplex genotyping of plurality of target nucleic acids have been fully capable at the time the invention was made, as well as the quantitation of nucleic acid target variants (which are two different sequences), which was demonstrated by Amexis et al. as well as Ross et al.

Therefore the invention as claimed is deemed *prima facie* obvious over the cited references and the rejection is maintained for the reasons already of record.

Conclusion

No claims are allowed.

Applicants' traversal to the examiner's position taken with regard to the multiplex MALDI-TOF detection being well known in the art (i.e., official notice) results in the citation of an evidentiary reference so as to substantiate the Examiner's position.

MPEP 2144.03(D) states the following in such a situation:

“If the examiner adds a reference in the next Office action after applicant's rebuttal, and the newly added reference is added only as directly corresponding evidence to support the prior common knowledge finding, and it does not result in a new issue or constitute a new ground of rejection, the Office action may be made final.”

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Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

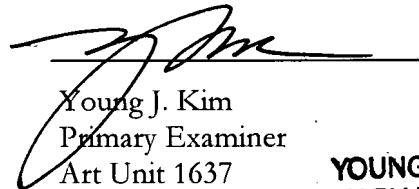
If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED**, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the

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status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Young J. Kim
Primary Examiner
Art Unit 1637
11/16/2007

**YOUNG J. KIM
PRIMARY EXAMINER**

YJK